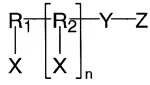
IN THE CLAIMS

Please all prior versions and claims listing with the following claims listing:

Claims listing

1. (withdrawn) A heparin-binding growth factor (HBGF) analog of formula I:



I

wherein:

each X is a peptide chain that (i) has a minimum of three amino acid residues, (ii) has a maximum of about fifty amino acid residues, and (iii) binds a heparin-binding growth factor receptor (HBGFR);

R_1 is an amino acid residue, wherein X is covalently bonded through the N-terminus of R_1 or through a side chain of R_1;

R_2 is a trifunctional alpha amino acid residue, wherein X is covalently bonded through a side chain of R_2;

Y is a linker comprising a chain from 0 to about 50 atoms covalently bonded to R_1 and Z when n=0, or to R_2 and Z when n=1;

Z is a non-signaling peptide chain that comprises a heparin binding domain, comprising an amino acid sequence that comprises (i) a minimum of one heparin binding motif, (ii) a maximum of about ten heparin binding motifs, and (iii) a maximum of about thirty amino acids; and,

n is 0 or 1, wherein when n=1 the peptide chains X are identical.

2. (withdrawn) The heparin-binding growth factor analog of claim 1 wherein X and Z are synthetic peptide chains.

3. (withdrawn) The heparin-binding growth factor analog of claim 1 or 2 wherein Y further comprises a linker that (i) is hydrophobic, (ii) comprises a chain of a minimum of about 9 and a maximum of about 50 atoms, and (iii) is not found in the natural ligand of the heparin-binding growth factor receptor (HBGFR) which X binds.

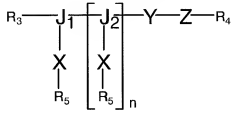
4. (withdrawn) The heparin-binding growth factor analog of claim 1 or 2 wherein R_1 is a trifunctional amino acid residue, wherein X is covalently bonded through a side chain of R_1.

5. (withdrawn) The heparin-binding growth factor analog of claim 1 or 2 wherein the heparin-binding growth factor analog has an avidity for heparin such that the synthetic heparin-binding growth factor analog binds heparin in 0.15 M NaCl, but is eluted by 1 M NaCl.

6. (withdrawn) The heparin-binding growth factor analog of claim 1 or 2, consisting essentially of a molecule of formula (I).

7. (withdrawn) The synthetic heparin-binding growth factor analog of claim 1 or 2, consisting of a molecule of formula (I).

8. (original) A heparin-binding growth factor (HBGF) analog of formula II:



II

wherein:

R_3 and R_5 are each independently NH_2, an acyl group with a linear or branched C_1 to C_{17} alkyl, aryl, heteroaryl, alkene, alkenyl or aralkyl chain including an N-terminus NH_2, NH_3^+, NH group or a corresponding acylated derivative, or is an amino acid, a dipeptide or a tripeptide with an N-terminus NH_2, NH_3^+, NH group or a corresponding acylated derivative;

R_4 is -OH, NH_2, NH-R_6, or is an amino acid, a dipeptide or a tripeptide with a C-terminus -OH, NH_2, or NH-R_6;

R_6 is an aliphatic C_1 to C_{17} chain;

each X is a peptide chain that (i) has a minimum of three amino acid residues, (ii) has a maximum of about fifty amino acid residues, and (iii) binds a heparin-binding growth factor receptor (HBGFR);

J_1 and J_2 are each independently a trifunctional alpha amino acid residue, wherein each X is covalently bonded through a side chain of J_1 or J_2;

Y is a linker comprising a chain from 0 to about 50 atoms covalently bonded to J_1 and Z when n=0, or to J_2 and Z when n=1;

Z is a non-signaling peptide that comprises a heparin binding domain, comprising an amino acid sequence that comprises (i) a minimum of one heparin binding motif, (ii) a maximum of about ten heparin binding motifs, and (iii) a maximum of about thirty amino acids; and,

n is 0 or 1, wherein when n=1 the synthetic peptide chains X are identical.

9. (original) The heparin-binding growth factor analog of claim 8 wherein X and Z are synthetic peptide chains.

10. (original) The heparin-binding growth factor analog of claim 9 which is a synthetic heparin-binding growth factor analog.

11. (original) The heparin-binding growth factor analog of claim 8, 9 or 10 wherein Y further comprises a linker that (i) hydrophobic, (ii) comprises a chain of a minimum of about 9 and a maximum of about 50 atoms, and (iii) is not found in the natural ligand of the heparin-binding growth factor receptor (HBGFR) which X binds.

12. (original) The heparin-binding growth factor analog of claim 8, 9 or 10 wherein the heparin-binding growth factor analog has an avidity for heparin such that the heparin-binding growth factor analog binds heparin in 0.15 M NaCl, but is eluted by 1 M NaCl.

13. (original) The heparin-binding growth factor analog of claim 8, 9 or 10 wherein binding of the heparin-binding growth factor analog to the heparin-binding growth factor receptor initiates a signal by the heparin-binding growth factor receptor.

14. (original) The heparin-binding growth factor analog of claim 8, 9 or 10 wherein binding of the heparin-binding growth factor analog to the heparin-binding growth factor receptor blocks signaling by the heparin-binding growth factor receptor.

15. (original) The heparin-binding growth factor analog of claim 8, 9 or 10 wherein J_1 and, if n = 1, J_2 is a diamine amino acid residue.

16. (original) The heparin-binding growth factor analog of claim 15 wherein the diamine amino acid residue is a 2,3 diamino propionyl amino acid residue.

17. (original) The heparin-binding growth factor analog of claim 15 wherein the diamine amino acid residue is lysine.

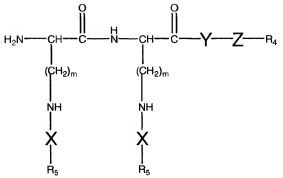
18. (original) The heparin-binding growth factor analog of claim 15 wherein the diamine amino acid residue is ornithine.

19. (original) The heparin-binding growth factor analog of claim 8, 9 or 10 wherein the covalent bond between X and J_1 or, if n=1, J_2, comprises a peptide, disulfide, thioether, Schiff base, reduced Schiff base, imide, secondary amine, carbonyl, urea, hydrazone or oxime bond.

20. (original) The heparin-binding growth factor analog of claim 8, 9 or 10 wherein the side chain of J_1 and, if n=1, J_2, comprises a reactive carboxyl group.

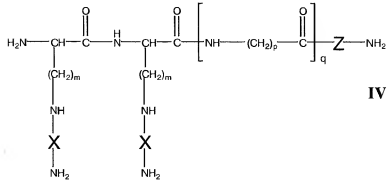
21. (withdrawn) The heparin-binding growth factor analog of claim 8, 9 or 10 of formula III:

III



wherein m is from 1 to about 10.

22. (withdrawn) The heparin-binding growth factor analog of claim 21 of formula IV:



IV

wherein p is from 1 to about 10 and q is from 1 to about 20.

23. (withdrawn) The heparin-binding growth factor analog of claim 22 wherein p is 5, q is three, Z is SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4 or SEQ ID NO:5, and X is SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20 or SEQ ID NO:21.

24. (withdrawn) The heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22 wherein the peptide chain X has a minimum of approximately five amino acid residues.

25. (withdrawn) The heparin-binding growth factor analog of claim 24 wherein the peptide chain X has a minimum of approximately nine amino acid residues.

26. (withdrawn) The heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22 wherein the peptide chain X has a maximum of approximately thirty three amino acid residues.

27. (original) The heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22 wherein the peptide chain X comprises an amino acid sequence found in a heparin-binding growth factor.

28. (original) The heparin-binding growth factor analog of claim 27 wherein the heparin-binding growth factor is a hormone, a cytokine, a lymphokine, a chemokine or an interleukin.

29. (original) The heparin-binding growth factor analog of claim 29 wherein X comprises an amino acid sequence found in any of FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, FGF-15, FGF-16, FGF-

17, FGF-18, FGF-19, FGF-20, FGF-21, FGF-22, FGF-23, HBBM (heparin-binding brain mitogen), HB-GAF (heparin-binding growth associated factor), HB-EGF (heparin-binding EGF-like factor) HB-GAM (heparin-binding growth associated molecule, also known as pleiotrophin, PTN, HARP), TGF-α (transforming growth factor-α), TGF-βs (transforming growth factor-βs), VEGF (vascular endothelial growth factor), EGF (epidermal growth factor), IGF-1 (insulin-like growth factor-1), IGF-2 (insulin-like growth factor-2), PDGF (platelet derived growth factor), RANTES, SDF-1, secreted frizzled-related protein-1 (SFRP-1), small inducible cytokine A3 (SCYA3), inducible cytokine subfamily A member 20 (SCYA20), inducible cytokine subfamily B member 14 (SCYB14), inducible cytokine subfamily D member 1 (SCYD1), stromal cell-derived factor-1 (SDF-1), thrombospondins 1, 2, 3 and 4 (THBS1-4), platelet factor 4 (PF4), lens epithelium-derived growth factor (LEDGF), midikine (MK),macrophage inflammatory protein (MIP-1), moesin (MSN), hepatocyte growth factor (HGF, also called SF), placental growth factor, IL-1 (interleukin-1), IL-2 (interleukin-2), IL-3 (interleukin-3), IL-6 (interleukin-6), IL-7 (interleukin-7), IL-10 (interleukin-10), IL-12 (interleukin-12), IFN-α (interferon-α), IFN-γ (interferon-γ), TNF-α (tumor necrosis factor-α), SDGF (Schwannoma-derived growth factor), nerve growth factor, neurite growth-promoting factor 2 (NEGF2), neurotrophin, BMP-2 (bone morphogenic protein 2), OP-1 (osteogenic protein 1, also called BMP-7), keratinocyte growth factor (KGF), interferon-γ inducible protein-20, RANTES, and HIV-tat-transactivating factor, amphiregulin (AREG), angio-associated migratory cell protein (AAMP), angiostatin, betacellulin (BTC), connective tissue growth factor (CTGF), cysteine-rich angiogenic inducer 61 (CYCR61), endostatin, fractalkine/neuroactin, glial derived neurotrophic factor (GDNF), GRO2, hepatoma-derived growth factor (HDGF), and granulocyte-macrophage colony stimulating factor (GMCSF).

30. (original) The heparin-binding growth factor analog of claim 29 wherein X comprises an amino acid sequence found in a fibroblast growth factor (FGF).

31. (original) The heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22 wherein the peptide chain X comprises an amino acid sequence not found in the natural heparin-binding growth factor receptor ligand.

32. (original) The heparin-binding growth factor analog of claim 31 wherein the heparin-binding growth factor analog binds an FGF receptor.

33. (original) The heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22 wherein the heparin-binding growth factor analog is an agonist of the heparin-binding growth factor receptor.

34. (original) The heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22 wherein the heparin-binding growth factor analog is an antagonist of the heparin-binding growth factor receptor.

35. (original) The heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22 wherein the heparin-binding growth factor analog is a positive modulator of the biological response to a heparin-binding growth factor.

36. (original) The heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22 wherein the heparin-binding growth factor analog is a negative modulator of the biological response to a heparin-binding growth factor.

37. (original) The heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22 wherein the peptide chains X are cross-linked or cyclized.

38. (original) The heparin-binding growth factor analog of claim 37 wherein the peptide chains X are cross-linked or cyclized by at least one disulfide, peptide, or thioether bond.

39. (original) The heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22 wherein Y comprises between one and about thirty-three ethylene glycol units.

40. (original) The heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22 wherein Y comprises a branched or unbranched, saturated or unsaturated alkyl chain of between one and about twenty carbon atoms.

41. (original) The heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22 wherein Y comprises $[NH_2\text{-}(CH_2)_pCO]_q$ wherein p is from 1 to about 10 and q is from 1 to about 20.

42. (original) The heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22 wherein Y comprises a peptide sequence comprising from one to about 16 Gly residues.

43. (original) The heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22 wherein each heparin binding motif of Z is BxBB, or BBBxxB, wherein each B is independently lysine, arginine, ornithine, or histidine, and x is a naturally occurring amino acid.

44. (original) The heparin-binding growth factor analog of claim 43 wherein Z comprises at least two heparin-binding motifs.

45. (original) The heparin-binding growth factor analog of claim 43 wherein Z comprises at least five heparin-binding motifs.

46. (withdrawn) A pharmaceutical composition comprising the heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22 or a pharmaceutically acceptable salt thereof and a pharmaceutical carrier.

47. (withdrawn) A method for treating a mammal that is exposed to a harmful dose of radiation or a chemotherapeutic agent, the method comprising administering to the mammal an effective dose of a heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22.

48. (withdrawn) A method for treating a mammal that is exposed to a harmful dose of radiation or a chemotherapeutic agent, the method comprising administering to the mammal an effective dose of a heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22 wherein X binds an FGF receptor.

49. (withdrawn) The method of claim 47or 48 wherein the dose of radiation or chemotherapeutic agent is sufficient to cause mucositis, G.I. syndrome, or radionecrosis.

50. (withdrawn) The method of claim 48 wherein the FGF receptor is an FGF-7 receptor.

51. (withdrawn) A method for stimulating growth factor receptor signaling in a cell, the method comprising contacting the cell with an effective amount of a heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22.

52. (withdrawn) The method of claim 51 wherein the signaling stimulates proliferation of the cell.

53. (withdrawn) The method of claim 52 wherein the cell is part of a mammal.

54. (withdrawn) A method for delivering an active heparin-binding growth factor analog to a mammal, the method comprising:

providing a medical device coated on the surface thereof via non-covalent bonds with a synthetic heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22; and

placing the medical device onto a surface of, or implanting the medical device into, the mammal.

55. (withdrawn) The method of claim 54 wherein the medical device is a suture, graft material, wound covering, nerve guide, bone wax, aneurysm coil, embolization particle, microbead, stint, dental implant, or bone prosthesis, a tissue scaffold or a controlled release drug delivery device.

56. (withdrawn) The method of claim 54 wherein the non-covalent bonds are associations between the heparin-binding domain of the synthetic heparin-binding growth factor analog and a heparin-containing compound bound to the surface of the medical device.

57. (withdrawn) The method of claim 56 wherein the heparin-containing compound is benzyl-bis(dimethylsilylmethyl)oxycarbamoyl-heparin.

58. (withdrawn) The method of claim 54 wherein the surface of the medical device is stainless steel, titanium, platinum, tungsten, ceramics, polyurethane, polytetrafluoroethylene, extended polytetrafluoroethylene, polycarbonate, polyester, polypropylene, polyethylene, polystyrene, polyvinyl chloride, polyamide, polyacrylate, polyurethane, polyvinyl alcohol, polycaprolactone, polyactide, polyglycolide, polysiloxanes, natural rubbers, artificial rubbers, block polymers, or copolymers of block polymers.

59. (withdrawn) The method of claim 58 wherein the polysiloxane is 2,4,6,8-tetramethylcyclotetrasiloxane.